REMARKS/ARGUMENTS

In the present amendment Claim 31 has been amended and Claims 36 and 37 have been added anew. Thus, following entry of the present amendment, Claims 31, 32, 34, 36, and 37 are pending in the present application and under consideration.

Support for the amendment and support for the new claims are replete throughout the specification. In particular, Claim 31 has been amended to clarify that the cancer cell overexpress a "Dvl-3 protein." Support for this amendment is found, e.g., *inter alia*, on page 6, lines 5-8; page 40, lines 11-15; page 42, lines 8-9; page 43, lines 8-11; page 44, lines 21-28; page 46, lines 1-8; and page 48, line 20 to page 49, line 17. Further, Claim 31 has been amended to recite the phrase "wherein growth of said cancer cell is inhibited." Support for this amendment can be found in the specification, e.g., *inter alia*, in Figure 9 and Example 11, and in particular, on page 49, lines 12-14.

New Claim 36 depends on claim 31 and is directed to a mesothelioma cell. Support for this amendment is found, e.g., *inter alia*, on page 4, lines 13-14 and 17-18; page 18, lines 1-4 and Figure 8; page 18, lines 18-23; page 42, lines 8-9; page 44, lines 21-28; and page 46, lines 1-8.

New Claim 37 depends on Claim 31 and is directed to a breast cancer cell. Support for this amendment is found, e.g., *inter alia*, on page 18, lines 18-23; page 42, lines 8-9; and page 43, lines 3-11.

No new matter was introduced by the amendment as filed.

Priority

Applicants acknowledge the Examiner's determination of the priority date for pending claims 31, 32, and 34 as July 31, 2003, the filing date of Applicant's provisional application Ser. No. 60/491,350.

Free Of Prior Art

It is noted that the Examiner did not cite any prior art reference against claims 31, 32, and 34.

Sequence Compliance

The Examiner objected to the specification and claims for failing to adhere to the requirements of the sequence rules. In particular, the Examiner noted that Applicants allegedly have not provided a statement that the computer readable format submitted and the paper copy of the sequence listing are the same. Applicants respectfully wish to draw the Examiner's attention to the "Communication Under 37 C.F.R. §§ 1/821-1.825 And Preliminary Amendment" submitted August 9, 2004. Therein Applicants state:

> "The information contained in the computer readable disk was prepared through the use of the software program "PatentIn" and is identical to that of the paper copy. This amendment contains no new matter."

Thus, the sequence listing information recorded in computer readable form is identical to the written sequence listing. Applicants respectfully request withdrawal of the objection.

Specification

The Examiner objected to the disclosure because it contains embedded hyperlinks and/or other form of browser-executable code on page 9, line 30 and page 11, line 1. The specification has been amended to remove the embedded hyperlinks. In view of this amendment, Applicants respectfully request withdrawal of the objection.

Claim Rejection - 35 USC § 112, Second Paragraph

The Examiner rejected Claims 31, 32, and 34 under 35 U.S.C. § 112, second paragraph. According to the Examiner, Claim 31 is vague and indefinite for the recitation of the term "a Dvl protein." The Examiner correctly points out that there are three known isoforms of

Dvl (Dvl-1, Dvl-2, and Dvl-3). According to the Examiner, it is not clear if the claims are drawn to cancer cells that overexpress one Dvl protein, two Dvl proteins, or all three Dvl proteins.

The rejection is respectfully traversed.

A. *The Legal Standard*

Under 35 U.S.C. § 112, second paragraph, a claim must particularly point out and distinctly claim the subject matter which the applicant regard as his invention. *See* 35 U.S.C. § 112, second paragraph. This statutory mandate is met when "one skilled in the art would understand the bounds of the claim when read in light of the specification." *See Personalized Media Communications, LLC v. International Trade Commission et al.*, 161 F.3d 696, 48 USPQ2d 1880 (Fed. Cir., 1998). "If the claims read in light of the specification reasonably apprise those skilled in the art of the scope of the invention, §112 demands no more." *See id.*, quoting *Miles Lab., Inc. v. Shandon, Inc.* 997 F.2d 870, 238 USPQ2d 1123 (Fed. Cir., 1993).

B. *Claim 31 is not Vague or Indefinite as Amended*

Applicants wish to draw the Examiner's attention to page 6, line 5 of the application where Applicants state that "Dvl proteins include, for example Dvl-1, Dvl-2, and Dvl-3." Without acquiescing to the propriety of the objection, Applicants have amended Claim 31 to recite a cancer cell that overexpresses a "Dvl-3 protein." Accordingly, Applicants respectfully submit that Claim 31 as amended is not indefinite or vague and request withdrawal of the rejection.

Claim Rejection - 35 USC § 112, Fist Paragraph

The Examiner rejected Claims 31, 32, and 34 under 35 U.S.C. §112, first paragraph, as allegedly failing to comply with the written description requirement. Specifically, the Examiner noted that Claim 31 is drawn to a method of inhibiting the growth of a cancer cell that overexpresses a Dvl protein, the method comprising contacting a cell with an agent that inhibits Dvl expression. Referring to page 4, lines 11-14 of the specification, the Examiner finds support for an agent that inhibits Dvl expression as a small molecule or a siRNA. Further, the

Examiner noted that Applicants did not provide a sufficient description of a representative number of agents to show that Applicants were in possession of a genus that includes e.g., any siRNAs that inhibit any of the Dvl proteins.

The rejection is respectfully traversed.

A. *The Legal Standard*

With regard to the "written description" requirement, the specification must describe the invention in sufficient detail that one skilled in the art can conclude that the "inventor invented the claimed invention." *University of California v. Eli Lilly and Co.*, 119 F.3d 1559, 1566, 43 USPQ2d 1398, 1404 (Fed. Cir., 1997 (quoting *Lockwood v. American Airlines, Inc.*, 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (1997). Also, a written description for a chemical genus "requires a precise definition, such as by *structure*, formula, chemical name or *physical properties*. (emphasis added) *Id* at 1405. In other words, an applicant's specification "must ... convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention." *Vas-Cath Inc. v. Mahurkar*, 935 F.2d 1555, 1563-4, 19 USPQ2d 1111, 1117 (Fed. Cir., 1991); see also, *Union Oil Co. v. Atlantic Richfield Co.*, 208 F.3d 989, 997 (Fed. Cir., 2000). According to the MPEP §2163.02, an objective standard for determining compliance with the written description requirement is, "does the description clearly allow persons of ordinary skill in the art to recognize that he or she invented what is claimed." *In re Gosteli*, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir., 1989). It is important to note in applying the "written description" requirement that "a patent need not teach, and preferably omits, what is well known in the art." *Hybritech Incorporated v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384, 231 USPQ 81, 94 (Fed. Cir., 1986). "The description need only describe in detail which is new or not conventional." *Id.* Further, whether an applicant has provided adequate written description, either explicitly or inherently, must be determined from the disclosure considered as a whole. *Reiffin v. Microsoft Corp.*, 214 F./3d 1342, 1345, 54 USPQ2d 1915, 1917 (Fed. Cir.,2000).

B. *Applicants' Specification Conveys with Reasonable Clarity to Those Skilled in the Art that Applicants were in Possession of the Invention*

Applicants describe that disheveled (Dvl) is a positive mediator of Wnt signaling positioned downstream of the frizzled receptors and upstream of βcatenin (e.g., page 2, lines 27-28; page 25, lines 23-32). Applicants have discovered that many cancers that overexpress a Wnt protein also overexpress a Dvl protein, and in particular a Dvl-3 protein. As noted above, Applicants have amended Claim 31 to recite "a Dvl-3 protein." In the Wnt signaling cascade, Dvl is positioned downstream of Wnt/ Therefore, an agent that inhibits Dvl expression, or Dvl-3 expression, is an agent that modulates Wnt activity as described, e.g., on page 26, lines 2-4. Such agents include nucleic acids inhibiting Dvl-3 expression. Applicants' specification also describes various inhibitors of Dvl gene expression and specifically states on page 27, lines 7-12:

> "In one aspect of the present invention, inhibitors of the Wnt signaling pathway, *e.g.*, ***Dvl*** inhibitors, can comprise nucleic acid molecules that inhibit expression of the target protein in the pathway. Conventional viral and non-viral based gene transfer methods can be used to introduce nucleic acids encoding engineered polypeptides, e.g., dominant negative forms of the protein, in mammalian cells or target tissues, or alternatively, nucleic acids, e.g., inhibitors of target protein expression, such as siRNAs or anti-sense RNAs." (emphasis added)

As such, one of ordinary skill in the art would appreciate that agents inhibiting Dvl-3 expression are not limited to small molecules or siRNAs. Rather, one of skill in the art would appreciate that nucleic acids inhibiting Dvl-3 expression include, e.g., Dvl-3 small interfering RNA (siRNA), Dvl-3 micro RNA (miRNA), Dvl-3 short hairpin RNA (shRNA) and Dvl-3 antisense RNA, and the like.

As shown in Figure 9 and Example 11 of Applicants' specification, Applicants describe a working example showing growth suppression of a cancer cell line by contacting the cancer cell with Dvl siRNA, i.e., an agent that inhibits Dvl expression. As described by Applicants, several cancer cells, including the cell line used for the Dvl siRNA experiment in Figure 9 and Example 11, showed down-regulation of Dvl-3 after anti-Wnt-1 monoclonal antibody treatment showing that prior to such treatment these cancer cells overexpressed Dvl-3.

The Dvl-3 siRNA experiment described in Figure 9 and Example 11 shows that "[a]fter siRNA treatment, expression of dvl-3 was suppressed." (e.g., page 49, lines 9-10)

Applicants further describe in their application that nucleic acid and protein Dvl sequences are known from a variety of species, including mouse and human and that exemplary human Dvl-1, Dvl-2, and Dvl-3 protein sequences are available under reference sequences NP_004412, NP_004413, and NM_004414, respectively (page 6, lines 5-8). From these GenBank referenced, one of skill in the art can identify the respective nucleotide sequences and design siRNA as further discussed herein. For example, the Dvl-3 protein sequence referenced in NM_004414 directly leads one of skill in the art to the Dvl-3 nucleotide sequence as referenced by the GenBank reference NM-004423. Using the Dvl-3 nucleotide sequence of NM_004423 a representative number of Dvl-3 siRNA species having distinguishing identifying characteristics and falling within the scope of the claimed genus can be obtained. The availability of the published Dvl-3 nucleotide sequence (NM_004423) need not be disclosed in Applicants' specification. *Hybritech Inc.* at 1384.

Applicants describe in detail the performance of RNA interference experiments (e.g., specification on page 36, lines 9-17; page 42, line 32 to page 43, line 11; page 49, lines 5-17; and Figure 9). As one of skill in the art would appreciate, inhibition of protein expression by a nucleic acid, such as a siRNA or antisense RNA, is based on a method well known in the art and involves simple base pairing, i.e., hybridization, of an inhibiting nucleic acid and the mRNA encoding a target protein. This is a description of structural and physical properties consistent with the written description requirement of the patent laws. A skilled artisan would recognize that the genus of agents useful in the claimed methods can well be described by their ability to bind to a Dvl-3 nucleic acid sequence. As such the skilled artisan, contrary to the Examiner's position, must not envision a detailed chemical structure of the encompassed genus. A variety of different Dvl-3 nucleic acid inhibitors based on nucleic acid information of the published Dvl-3 nucleotide sequence can be obtained by one of skill in the art as discussed further herein, following the disclosure of Applicant's specification.

The above description clearly allows persons of ordinary skill in the art to recognize what he or she invented is what is claimed. *In re Gosteli,* 10 USPQ 2d 1614, 1618

(Fed. Cir., 1989). As such, Applicants have conveyed with reasonable clarity to those skilled in the art that, as of the filing date sought, they were in possession of the invention." *Vas-Cath Inc. v. Mahurkar*, 935 F.2d 1555, 1563-4, 19 USPQ2d 1111, 1117 (Fed. Cir., 1991). Applicants respectfully request the rejection of the claims under 35 U.S.C. § 112, first paragraph, be withdrawn.

Claim Rejection - 35 USC § 112, Fist Paragraph

The Examiner rejected Claims 31, 32, and 34 under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the enablement requirement.

The rejection is respectfully traversed.

A. *The Legal Standard*

The test for enablement is "whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent [application] coupled with information known in the art without undue experimentation." *United States v. Telectronics, Inc.*, 857 F.2d 778, 785, 8 USPQ2d 1217 (Fed. Cir., 1988); *Genentech, Inc. v. Novo Nordisk A/S*, 108 F.3d 1361, 1365, 42 USPQ2d 1001 (Fed. Cir., 1997); *In re Vaeck*, 947 F.2d 488, 495, 20 USPQ2d 1438 (Fed. Cir., 1991). The factors to be considered in determining whether undue experimentation is required include: (1) the breadth of the claims, (2) the nature of the invention, (3) the state of the prior art, (4) the level of ordinary skill, (5) the level of predictability in the art, (6) the amount of direction provided by the inventor, (7) the existence of working examples, and (8) the quantity of experimentation needed to make or use the invention. *In re Wands* 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir.,1988).

B. *One Reasonably Skilled in the Art Could Make or Use the Invention from the Disclosures in the Patent Application Coupled with Information Known in the Art without Undue Experimentation*

Applicants respectfully remind the Examiner of the following position of the court stated *In re Wands*:

> ...a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed.

In re Wands, 8 USPQ2d 1400 (Fed. Cir., 1988) (citing *In re Angstadt*, 190 USPQ 214 (CCPA 1976).

For the Examiner's convenience, the *In re Wands* factors are addressed in the order in which they were presented in the Office Action. As discussed below, the Examiner did not meet his burden to demonstrate that Applicants claims 31, 32, and 34 fail to comply with the enablement requirement.

The breadth of the claims (1) and the nature of the invention (2)

Aberrant Wnt signaling has been described in a variety of human cancers (e.g., specification at page 2, lines 9-24). Applicants describe that disheveled (Dvl) is a positive mediator of Wnt signaling positioned downstream of the frizzled receptors and upstream of βcatenin (e.g., page 2, lines 27-28; page 25, lines 23-32). Applicants have discovered that many cancers that overexpress a Wnt protein also overexpress a Dvl protein, and in particular a Dvl-3 protein. As noted above, Applicants have amended Claim 31 to recite "a Dvl-3 protein."

Thus, the amended claims are drawn to a method of inhibiting the growth of a cancer cell that overexpresses a Dvl-3 protein by contacting the cancer cell with an agent that inhibits Dvl-3 expression. Therefore, the amended claims no longer encompass a method utilizing an agent that inhibits Dvl expression, but rather an agent that inhibits Dvl-3 expression.

The state of the prior art (3), the level of ordinary skill (4), and the level of predictability in the art (5)

The Examiner cited Okino *et al.* for the teaching that members of the Dvl protein family may have different functions and are expressed in different cell types. In view of the amendment of Claim 31 to recite a "Dvl-3 protein," this part of the Examiner's argument is moot.

The Examiner further argues that the art teaches that mRNA levels are not always correlated with gene amplification and could be the result of transcriptional activation by hypo-

methylation of promoter regions and transactivation by other cellular molecules. This argument is not a convincing argument for arguing non-enablement. Whether Dvl-3 overexpression in a cell is the result of gene amplification or transcriptional activation by hypo-methylation of promoter regions, as discussed by the Examiner, is not relevant for Applicants' invention.

In addition, the Examiner cites Van Gijn *et al.* for the teaching that overexpression of Dvl-1 in transformed kidney cells (e.g., Cos-1 cells) results in apoptosis. Again, in view of Applicants amendment of Claim 31 to recite a "Dvl-3 protein," this part of the Examiner's argument is also moot.

The Examiner did not meet his burden showing that the state of the prior art and the level of predictability in the art is low. Rather, the state of the art in designing a nucleic acid inhibiting a nucleic acid encoding a target protein was high in July 2003, the accorded priority benefit of Applicants' claims. For example, Elbashir *et al.*, (*EMBO J.*, 20(23):6877-6888 (2001)) teaches synthetic, short interfering RNAs (siRNAs) and their requirement regarding length, structure, chemical composition and sequence in order to mediate efficient RNA interference.

Elbashir *et al.* (*Methods* 26(2):199-213 (2002)), as cited in Applicants' specification (e.g., on page 36, line 15), provides a collection of protocols for siRNA-mediated knockdown of mammalian gene expression and eludes to the "robustness of the siRNA knockdown technology." Additional guidance for the design of siRNAs is provided by Amarzguioui *et al.* (*Nucl. Acids Res.* (31(2):589-595 (2003)).

Further, Harborth *et al.* (*Antisense Nucleic Acid Drug Dev.* 13(2):83-105 (2003)) address the predictability of siRNA inhibition and find that 26 of 44 tested standard 21-23 nucleotide (nt) siRNA duplexes reduced protein expression by at least 90%, and only two duplexes reduced protein expression to <50%. Also Semizarov *et al.* (*Proc. Natl. Acad. Sci. USA*, 100(11):6347-6352 (2003)) conclude that siRNA is a highly specific tool for targeted gene knockdown. For the convenience of the Examiner, the references cited herein are included in a supplemental information disclosure statement submitted herewith.

Thus, the state of the art designing nucleic acids, such as siRNAs, based on a known target sequence, for efficient inhibition of a target protein expression and the level of ordinary skill is high. Further, there is a high predictability in the art.

The amount of direction provided by the inventor (6) and the existence of working examples (7)

Applicants provides references and a protocol as guidance for performing siRNA inhibition experiments (e.g., page 36, lines 9-17; page 49, lines 5-17; Figure 9). Further, as acknowledged by the Examiner, Example 11 of Applicants' specification describes a method of inhibiting the growth of a lung cancer cell line, H1703, using siRNA against Dvl-3. In view of the present amendment of Claim 31 to recite a cancer cell that overexpresses "a Dvl-3 protein" and an agent that inhibits "Dvl-3 expression," Example 11 provides support commensurate in scope with the claims as amended.

As provided and discussed, Dvl-3 siRNAs inhibiting Dvl-3 expression can be designed by one of skill in the art based on the published Dvl-3 nucleotide reference (e.g., GenBank reference NM_004423) and the guidance provided by the references provided herein which were available prior to the accorded priority date of Applicants' claimed invention of July 2003.

Applicants' specification does not need to provide the structure of a Dvl-3 siRNA in order to satisfy the enablement requirement. "A patent need not teach, and preferably omits, what is well known in the art." *Hybritech Incorporated v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384, 231 USPQ 81, 94 (Fed. Cir., 1986). "The description need only describe in detail which is new or not conventional." *Id.*

Quantity of experimentation needed to make or use the invention based on the content of the disclosure (8)

In view of the above, it is clear that the quantity of experimentation required to perform the present invention, i.e., inhibiting a cancer cell by contacting the cancer cell with an agent that inhibits Dvl-3 expression is low. As outlined above, sufficient guidance is provided by Applicants' specification.

In summary, the Examiner did not meet his burden to show that Claims 31, 32, and 34 are not enabled by Applicants' specification coupled with the information known in the

art. The disclosure of Applicants' application easily fulfills standards set forth in *In re Wands* for permissible experimentation, being both routine and/or well described in the specification. One reasonably skilled in the art could make or use the invention from the disclosures in the patent application coupled with information known in the art without undue experimentation. Applicants respectfully request the rejection of the claims under 35 U.S.C. § 112, first paragraph, be withdrawn.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If a telephone conference would expedite prosecution of this application, the Examiner is invited to telephone the undersigned at 415-576-0200.

Respectfully submitted,

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